

REMARKS

In response to the Final Office Action with a mailing date of October 13, 2010, Applicants provide the above amendments and the following comments to accompany the Request for Continued Examination.

In the Office Action Claims 1-4, 6-17 and 13-19 are pending and stand rejected. In the instant response the pending claims are cancelled and new claims 40-95 are provided. No new subject matter is added.

Claims 40-79 are based on the prior claims as filed and/or amended as listed below and contain rewording and/or further amendment in some cases: Claim 40 corresponds to claim 1. Claim 41, dependent on claim 40, adds a further intermediate washing or rinsing step based on Examples 1 and 2 in combination with Examples 3-7. Claims 42-79 correspond to prior claims 2-39, except that the limitations of claims 35 and 39 have been reintroduced in claims 48 and 61, corresponding to prior claims 8 and 21, respectively; and limitations which were present in prior claims 34 and 38, corresponding to claims 74 and 78, have been moved to claims 75 and 79, dependant on claims 74 and 78, respectively.

Claims 80-96 are a parallel set of method (process) claims drawn to the polymerization step, which is step (ii) of the earlier claims.

The Examiner is requested to reconsider the application in view of the amended claims and discussion which follows.

In the previous prosecution, the Examiner has noted that the claim language is open ended and non-limiting, but this aspect has not been addressed. To obviate this issue, which seems to have hindered the progress of the prosecution, independent claims 40 and 54, corresponding to prior claims 1 and 14 have been reformulated to incorporate "consisting essentially of" for the chemical reaction steps to make it clear that the process of forming a graft polymer on the substrate is not open ended and non-limiting. The "comprising" language earlier in the claims then allows for further steps to modify the graft polymer, as disclosed in the application. It is believed that the claims formulated in this manner more accurately describe the disclosed invention.

Claim 41 further provides a washing or rinsing step between the separate chemical reaction steps of (i) covalently coupling the primary or secondary amines of the substrate surface with a thermally labile radical initiator and (ii) graft copolymerization of the monomers onto the radical generated by thermolysis of the attached radical initiator.

In addition, the prosecution of the application seems to have been hindered by misperceptions or mischaracterizations of the technical teachings of the instant application and of some of the cited references. In other words, there have been errors in characterizations of the basic factual inquiries regarding the scope and the contents of the prior art. In hopes of expediting the prosecution, technical aspects of the disclosures and their teachings are reviewed below prior to a detailed response to the Office Action.

The Instant Application:

To provide a context for the remarks, the instant application is briefly reviewed. The instant application discloses a solid substrate bearing primary or secondary amino groups to which are covalently coupled thermally labile radical initiators as a first reaction step (inter alia, page 2, line 28, through page 3, line 24; page 8; and claims 1 and 14). This is illustrated in Reaction Scheme 1 at page 8 in which thermally labile radical initiators bearing a carboxy group are coupled to the amino groups of a solid substrate bearing primary amino groups using an amide coupling reaction. The formation of the intermediate material bearing radical initiators coupled to the solid substrate is demonstrated in the examples in the form of macroporous acrylic beads (Example 1) and in the form of microporous hollow fiber membranes (Example 2). In each example, the resulting substrate acylated with thermally labile radical initiators is purified by washing away excess reagents, solvents and the other reaction products.

In the second reaction step, the initiator immobilized surface of covalently attached thermally labile radical initiators is thermally decomposed to provide covalently attached radicals (top right figure of Reaction Scheme 1) to which are polymerized one or more particular polymerizable monomers to afford a separating material product. This is illustrated in Reaction Schemes 1-3 showing the adjacent functional polymer chains grafted on the surface of the substrate (in which the amide bonds are not shown) and is demonstrated in Examples 3-7. Thus, the -NH-C(O)-R-C- groups derived from the covalently attached radical initiators coupled to the amines serve as an additional element in the form of intermediate chemical binding moieties to join (graft) the polymer chains to the solid substrate bearing primary or secondary amino groups.

Accordingly, the claims include, inter alia, claims to a separating material product made by such a process and to the method of producing the separating material product. The claims as now amended explicitly require covalently coupling the primary or secondary amines with a thermally labile radical initiator and inherently require that the

polymeric chain resulting from the thermally initiated graft copolymerization of the polymerizable monomers be attached to the remaining residue of the thermally labile radical initiator (the intermediate chemical binding moiety) attached to the amines.

In the Office Actions, claims have been rejected as obvious over Horl et al., US 5,556,708 (Horl) in view of Pitt et al., US 5,037,656 (Pitt); but there have been some misperceptions or mischaracterizations of the technical teachings of these references. Some comments on these patents and the prosecution follow.

Horl et al. US 5,556,708 (Horl):

The Horl application claims a method for grafting unsaturated monomers (component A) to nitrogen-containing polymers (component B) in an aqueous environment in the presence of the two reactants: carbon tetrachloride and a reducing agent selected from sodium dithionite, rongalite, hydrazine and ascorbic acid (the latter in the alkaline range). The necessity for carbon tetrachloride is demonstrated in Example 2 at column 20, lines 40-54. The necessity for sodium dithionite (or a suitable substitute reducing agent) is shown in Example 3 at column 20, lines 56-67. As pointed out at column 4, lines 39-41, the mechanism of the reaction is unknown:

The mechanism on which the process of the invention is based is different than that of the N halogenation described above and still cannot be explained at the present time.

Although component B is said to comprise polyamides, polysulfonamides, polyurethanes, and polymers having primary or secondary amino groups in a side chain, the method is demonstrated only for polyamides, specifically nylon 6.6 (Examples 1-8) and nylon 6 (Example 6).

Further, Horl states at column 12, lines 20-29:

The use of the process of the invention surprisingly makes it possible to achieve an increase in the resistance to chain degradation. Since the same result is achieved by means of the method described in a parallel application ... by grafting onto N-halogen polymers, from which it is known that the grafting takes place on the nitrogen, it is assumed that the same also applies to the process of the invention, so that the hydrogen atoms on the nitrogen are substituted entirely or partially by the grafted-on polymer chain.

Thus, although the structural nature of the product formed in the Horl disclosure is unknown, the only teaching available from Horl is that the polymer chain is

polymerized directly on some or all of the amide nitrogens of the polyamide. There is no description in Horl of an intermediate chemical binding moiety which is covalently bound to an amino group of any substrate and to which is bound a chain formed by polymerization of polymerizable monomers.

Pitt et al. US 5,037,656 (Pitt):

The Pitt application is drawn to (column 2, lines 34-41):

...a hydrophilic composite porous membrane comprising a porous substrate having a permanent coating grafted and/or deposited thereon for the entire porous membrane including the inner pore walls which coating has physical and chemical properties different from the bulk properties of the porous membrane and which contains a cell attachment and/or growth promoting composition.

and includes the following independent claims:

1. A composite porous thermoplastic membrane which comprises a porous first polymer substrate membrane having an average pore size between about 0.001 and 15 microns, said membrane being directly coated on its entire surface with a collagen and a cross-linked second polymer formed from a monomer polymerized in situ with a free radical initiator and cross linked in situ on said substrate, said composite porous membrane having essentially the same porous configuration as said porous membrane substrate.

9. The process for forming a composite porous membrane formed from a porous first polymer substrate having an average pore size between about 0.001 and 15 microns, said substrate being directly coated over its entire surface with a collagen and a cross-linked second polymer, said composite porous membrane having essentially the same porous configuration as said porous membrane substrate which comprises:

contacting said porous membrane with a solution of said collagen, a multifunctional monomer of said second polymer, and a free radical polymerization initiator under conditions to polymerize said monomer and to crosslink said second polymer over the entire surface of said porous polymer substrate under conditions to avoid plugging of said pores.

16. The process for forming a composite hydrophilic porous membrane formed from a porous polytetrafluoroethylene substrate having a pore size between about 0.001 and 15 microns, said substrate being directly coated over its entire surface with a collagen and a cross-linked second polymer, said composite porous membrane having essentially the same

porous configuration as said porous membrane substrate which comprises:

(a) washing said porous membrane substrate to wet the surfaces of the pores in said porous membrane; and

(b) contacting said porous membrane with a solution of a collagen, a monomer of said second polymer, a polymerization initiator and a cross-linking agent for said monomer under conditions to polymerize said monomer and to cross-link said second polymer over the entire surface of said porous polytetrafluoroethylene substrate under conditions to avoid plugging of said pores, said solution comprising between about 10 and 90 weight percent water and between about 80 and 10 weight percent of a water miscible organic solvent.

Although the description as cited above indicated the coating might be grafted on, the description expressly states (column 2, lines 46-48) that:

...the coating polymer is directly coated onto the porous substrate without the utilization of an intermediate binding chemical moiety.

A number of misperceptions or mischaracterizations of the technical teachings of the cited references have appeared in the prosecution.

As one example, in characterizing the disclosure of Horl, it has been repeatedly stated that Horl discloses as a step:

Covalently coupling the amino functional groups with a reducing agent (C8/L1-15, C11/L28-33 – the reducing agent would couple covalently with the amino functional groups due to chemical attraction when exposed in an aqueous or liquid environment with the reducing agent and utilizing a thermal activation, C11/L43-50);

It must be pointed out that the mechanism posited in the Office Actions is not supported by Horl (nor otherwise supported by any evidentiary support). As noted above, Horl states: "The mechanism ... still cannot be explained at the present time."

Horl at C8/L1-15 states:

Graft polymerization can be carried out both in liquid phase, that is, in a melt or solution, and in a solid phase, at which time the base polymer must generally be in a swollen form in order to make possible the access of the monomer to the chains of the base polymer. The swelling can take place either by means of the monomer itself or by means of a further component which does not participate itself [sic] in the polymerization. The grafting progresses in this instance from the surface to the

interior of the polymer. The case can occur thereby that the graft copolymer being produced is soluble in the grafting medium, which accelerates the progress of the grafting because the diffusion paths are not lengthened during the grafting.

Horl at C11/L28-33 states:

The preferred reducing agent for the application of the process of the invention is sodium dithionite as well as its daughter products such as e.g. rongalite. Other reducing agents such as hydrazine or ascorbic acid, the latter in the alkaline range, can also be used but are less preferred.

Horl at C11/ L43-50 states:

Rongalite, which is produced industrially as dithionite with formaldehyde, appears to be effective like dithionite itself in a quite similar manner and the addition of complexing Fe ions as well as the elevation of temperature essentially appears to bring about the release of dithionite.

These statements from Horl do not teach a residue covalently bound to an amino nitrogen to which covalently bound residue will be attached a polymerized chain of polymerizable monomers.

Furthermore, the thermal activation of the instant application occurs in the later polymerization step, not in the earlier step of covalently coupling of the amino functional groups with a thermally labile radical initiator.

It has been stated (Office Action of January 29, 2010, at page 11, line 8) that carbon tetrachloride is not a required component in the process of Horl. This statement is in direct opposition to the teachings of Horl mentioned above; and any explanation of the process of Horl must include the carbon tetrachloride as a reactant. Moreover, the statement that Horl at C4/L50-60 teaches carbon tetrachloride can be used to improve the solubility range is in error. The cited portion states at column 4, lines 52-63:

The process of the invention is advantageously carried out in water as reaction medium; however, media can also be considered which contain other components such as e.g. alcohols or ketones in addition to water, the monomer and carbon tetrachloride in order to broaden the solubility range of the monomer used. The limitation of the addition of organic solvents is given by the solubility of the reducing agent used, which decreases as the water content drops.

The solubility of carbon tetrachloride in water is approximately 0.08% by weight and is sufficient for carrying out the grafting.

Clearly, "water, the monomer and carbon tetrachloride" are required elements, and carbon tetrachloride is not being used to improve the solubility range.

Accordingly, the statement in the Office Action does not accurately characterize the teaching of Horl. Additionally, as pointed out in the response of June 17, 2009, at page 14, in footnote 1, Applicant respectfully submits that the Office has failed to provide "specific factual findings predicated on sound technical and scientific reasoning" to support the conclusion.

In characterizing the disclosure of Pitt, it has repeatedly been stated that Pitt discloses as a step:

Covalently coupling a thermally labile radical initiator to the membrane (C4/L30-40 – see exemplary compounds, specifically "4,4-azobis-(4-cyanovaleric acid)" – also see C3/L58-66

It must be pointed out that the step posited above does not accurately characterize the teaching of Pitt.

As noted above, Pitt teaches a "membrane being directly coated on its entire surface with a collagen and a cross-linked second polymer formed from a monomer polymerized in situ with a free radical initiator and cross linked in situ on said substrate..."

Pitt at C3/L58-66 states:

Subsequent to wetting the porous membrane, a reagent bath comprising the cell adhesion and growth promoting composition, a free radical polymerizable monomer, a polymerization initiator and cross-linking agent in solvent comprising water or water and a water miscible, polar, organic solvent for these constituents is contacted with the porous membrane under conditions to effect free radical polymerization of the monomer and coating on the porous membrane with a cross-linked polymer.

As to the initiators and cross-linking agents, Pitt at C4/L29-42 states:

Suitable initiators and cross-linking agents for the monomers set forth above are well known in the art. For example, when utilizing acrylates as the polymerizable monomer, suitable chemical polymerization initiators include ammonium persulfate, potassium persulfate, 4,4-azobis-(4-cyanovaleric acid), 2,2-azobis (2-amidinopropane) hydrochloride, potassium hydrogen persulfate or the like. In addition to chemical initiation, ultraviolet light, electron beam or cobalt-60 irradiation can be used to initiate polymerization. When utilizing acrylates of methacrylates or methacrylamides as the

polymerizable monomer, suitable cross-linking agents include difunctional acrylates, methacrylates or acrylamides such as tetraethylene glycol diacrylate, glycidyl acrylate or methylene bisacrylamide or the like.

At no place does Pitt disclose the formation of a covalent bond of its substrate membrane with 4,4-azobis-(4-cyanovaleric acid); the reagent is merely one of a list of radical initiators for polymerization and cross-linking the monomers and cross-linking agents forming the coating of the membrane. In fact, Pitt describes the coupling of monomers to coat "membranes such as polyamides (Nylon) or the like or hydrophobic membranes such as polytetrafluoroethylene, polycarbonate, polyvinylidene fluoride, polysulfones, polyether sulfones or the like." (Column 3, lines 16-19.) None of these surfaces exhibits primary (or secondary) amino groups. The only exemplification in Pitt is the coating of microporous polytetrafluoroethylene. Accordingly, there is no motivation provided in Pitt to encourage the formation of a covalent bond of its substrate membrane with 4,4-azobis-(4-cyanovaleric acid).

Moreover, as noted above, Pitt expressly states that the coating polymer is directly coated onto the porous substrate without the utilization of an intermediate binding chemical moiety.

Accordingly, the statement that Pitt teaches "covalently coupling a thermally labile radical initiator to the membrane" does not accurately characterize the teaching of Pitt.

Further, in the August, 2009, Office Action at page 12, it is stated, "the combination of Horl and Pitt provides for the radical initiator in solution with the amino functional and the monomer. Accordingly, there would be inherent covalent bonding occurring between the radical initiator and then the radical with the amino group and then linking it to the monomer." It is submitted that the proffered mechanism finds no support in the cited references or otherwise. Further, in applicant's claimed invention the radical initiator is not in solution with the monomer, it is bound to the substrate surface which is contacted with a solution of one or more polymerizable monomers.

In the Office Action, Claims 1-4, 6-17, 19-26, 35 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horl et al. (US 5,556,708) in view of Pitt et al. (US 5,037,656), in view of Sirvio et al. (US 5,532,311) and in view of Hodgdon (US 5,152,901). As discussed below, in view of the currently amended claims, Applicants respectfully traverse this basis for rejection because there is a failure to make a *prima facie* case of obviousness.

Horl and Pitt have been combined based on the rationale that each is concerned with the same field of endeavor, graft polymerization membrane structures. It is asserted that this is a very broad field and encompasses extremely different substrate membrane types in terms of composition, structure and geometry, extremely different grafting structures and process types, and also extremely different uses to which such grafted membranes may be put to the extent that it is not appropriate to include them together. Nevertheless, even if the references are combined, there is no way in which the instant invention can be derived from them. As noted above, the combination provides no suggestion or motivation for the covalent linkage of a thermally labile radical initiator to an amino group coupled to a substrate surface, followed by graft copolymerization of monomers onto the radical generated by thermolysis of the attached radical initiator.

Moreover, the product formed by the instant invention is not the same as or obvious over the product made by Horl. There is no evidence in Horl of an intermediate moiety derived from a thermally labile radical initiator between the nitrogen-containing polymer and the grafted polymer.

Sirvio et al. US 5,532,311 (Sirvio):

Sirvio discloses, inter alia, at column 1, lines 34-42:

a process for modifying the surface of an article that includes (a) treating the surface with (i) a first water-soluble polyalkylene amine, (ii) a water-soluble polymeric anionic compound, and (iii) a second water-soluble polyalkylene amine, all in the absence of crosslinking agents, to cream [sic, create] a primed surface; and (b) contacting the primed surface with a biologically active agent to bind the biologically active agent to the primed surface.

The biologically active agent such as heparan sulfate, hyaluronic acid, dermatan sulfate, chitosan, or derivatives thereof is intended to make the surface biocompatible, for example to make the surfaces that are in direct contact with blood or blood products nonthrombogenic. The binding of the biologically active agent to the primed surface may be ionic or covalent, preferably covalent. The covalent binding may be accomplished using a biological agent having free aldehyde groups which form a Schiff's base with an amine of the surface, which is then reduced to an amine, or alternatively, for certain biological agents not having free aldehyde groups, by using a carbodiimide coupling agent. The invention is illustrated using periodate oxidized heparin as a biological agent

having free aldehyde groups in solution with sodium cyanoborohydride to reduce the Schiff's base.

Because there is no thermally labile radical initiator covalently coupled in the Horl or Pitt process and no motivation or teaching to combine Horl and Pitt, the further addition of Sirvio cannot provide the motivation to couple a thermally labile radical initiator to a surface as an intermediate moiety to which a chain is polymerized.

Hodgdon. US 5,152,901 (Hodgdon):

Hodgdon is directed to "a highly crosslinked polyamine-polyamide polymerized upon a microporous polysulfone sheet and co-blended with a latex polymer having the ability to react with chlorine or other oxidants while processing feed streams for the separation of calcium (or magnesium) from sodium salts."

The fact that Hodgdon discloses a polyamine-polyamide does not provide any teaching necessary to provide the motivation to couple a thermally labile radical initiator to a surface as an intermediate moiety to which a chain is polymerized.

Accordingly, applicants respectfully request the withdrawal of the rejection of claims 1-4, 6-17, 19-26, 35 and 39 as being unpatentable over Horl et al. (US 5,556,708) in view of Pitt et al. (US 5,037,656), in view of Sirvio et al. (US 5,532,311) and in view of Hodgdon (US 5,152,901).

In the Office Action, Claims 27-30, 32 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horl et al. (US 5,556,708) in view of Pitt et al. (US 5,037,656), and further in view of Bell et al. (US 6,774,102). As discussed below, in view of the currently amended claims, Applicants respectfully traverse this basis for rejection because there is a failure to make a *prima facie* case of obviousness.

Bell et al. is directed to an endotoxin removal adsorbent, and a device and a method employing the endotoxin removal adsorbent for extracorporeal removal of endotoxin from whole blood.

As discussed above, "modified Horl" does not anticipate or make obvious the separating material of the instant claims. Thus, the use of the novel, nonobvious separating material of the instant invention cannot be obvious from the combination of Horl et al. in view of Pitt et al., and further in view of Bell et al.

Accordingly, applicants respectfully request the withdrawal of the rejection of claims 27-30, 32 and 36 as being unpatentable over Horl et al. (US 5,556,708) in view of Pitt et al. (US 5,037,656), and further in view of Bell et al. (US 6,774,102).

In the Office Action, Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Horl et al. (US 5,556,708) in view of Pitt et al. (US 5,037,656), in view of Sirvio et al. (US 5,532,311) and in view of Hodgdon (US 5,152,901) in view of Bell et al. (US 6,774,102), and further in view of Duggins (US 4,668,399). As discussed below, in view of the currently amended claims, Applicants respectfully traverse this basis for rejection because there is a failure to make a *prima facie* case of obviousness.

Duggins is directed to a hollow fiber plasmapheresis process employing certain materials commonly available for that use.

As discussed above, "modified Horl" does not anticipate or make obvious the separating material of the instant claims. Thus, the use of the novel, nonobvious separating material of the instant invention cannot be obvious from the combination of Horl et al. (US 5,556,708) in view of Pitt et al. (US 5,037,656), in view of Sirvio et al. (US 5,532,311) and in view of Hodgdon (US 5,152,901) in view of Bell et al. (US 6,774,102), and further in view of Duggins (US 4,668,399).

Accordingly, applicants respectfully request the withdrawal of the rejection of claim 31 as being unpatentable over Horl et al. (US 5,556,708) in view of Pitt et al. (US 5,037,656), in view of Sirvio et al. (US 5,532,311) and in view of Hodgdon (US 5,152,901) in view of Bell et al. (US 6,774,102), and further in view of Duggins (US 4,668,399).

In the Office Action, Claims 33-34 and 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horl et al. (US 5,556,708) in view of Pitt et al. (US 5,037,656), in view of Sirvio et al. (US 5,532,311) and in view of Hodgdon (US 5,152,901) and further in view of Steuck (US 4,613,533). (In the paragraphs following the rejection, "Bell et al." is used where it is clear that "Steuck" was intended. This is seen as merely an obvious word processing error.) As discussed below, in view of the currently amended claims, Applicants respectfully traverse this basis for rejection because there is a failure to make a *prima facie* case of obviousness.

Steuck is directed to a composite porous membrane formed from a porous polymeric membrane having desired bulk properties on which is directly coated a cross-linked polymer having desired surface properties and a process for its formation.

As discussed above, "modified Horl" does not anticipate or make obvious the separating material of the instant claims or the process for its formation. Addition of Steuck in no way makes up for the deficiency noted above; Steuck does not provide any teaching necessary to provide the motivation to couple a thermally labile radical initiator to a surface as an intermediate moiety to which a chain is polymerized.

Accordingly, applicants respectfully request the withdrawal of the rejection of claims 33-34 and 37-38 as being unpatentable over Horl et al. (US 5,556,708) in view of Pitt et al. (US 5,037,656), in view of Sirvio et al. (US 5,532,311) and in view of Hodgdon (US 5,152,901) in view of Bell et al. (US 6,774,102), and further in view of Steuck (US 4,613,533).

The Examiner is requested to reconsider the claims in view of the amendments provided above to reformulate and clearly direct the scope of the claims, and a notice of allowance for the amended claims is requested. Should it be useful to expedite the prosecution, the Examiner is invited to call.

Respectfully submitted,
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